REMARKS

Claims 1-52 are pending, having been provisionally restricted to species A, C, H and S of record.

The Examiner withdrew claims 53-97 as being drawn to a non-elected group. Applicants herein cancel claims 53-97 without prejudice and reserve the right to pursue this subject matter in one or more divisional applications.

The Examiner also withdrew claims 18-24, 26-43 and 45-47 as being drawn to non-elected species.

Claims 1-17, 25, 44 and 48-52 are, therefore, under current examination.

Applicants acknowledge the Examiner's objection of claims 3-6 as lacking appropriate 'colon' indicator for lists. Applicants have responsively amended these claims to obviate this rejection.

Applicants acknowledge the Examiner's rejection of claims 1-17, 25, 44 and 48-52, under 35 U.S.C. § 112 ¶*2* as being indefinite in the recitation of the term "disjunct." Applicants respectfully traverse this rejection.

Applicants acknowledge the Examiner's rejection of claims 1-4, 6-10 and 48, under 35 U.S.C. § 102(b) as being allegedly anticipated by Janousek et al. (*Molecular and General Genetics*, 250:483-490, 1996). Applicants have made clarifying amendments to the claims to obviate this rejection.

Applicants acknowledge the Examiner's rejection of claims 1, 2, 10-16, 25, 44, and 52, under 35 U.S.C. § 103(a) as being allegedly obvious Janousek et al. (*Molecular and General Genetics*, 250:483-490, 1996) in view of Curtis et al. (Annals of Human Genetics., 65:95-107, Jan. 2001). Applicants respectfully traverse this rejection based on the current amendments.

Applicants acknowledge the Examiner's rejection of claims 1, 10, 11, 13 and 17, under 35 U.S.C. § 103(a) as being allegedly obvious Janousek et al. (*Molecular and General Genetics*, 250:483-490, 1996) in view of Curtis et al. (Annals of Human Genetics., 65:95-107, Jan. 2001), and in further view of Spotorno et al. (*Evolution Biologica*, 4:37-62, 1990). Applicants respectfully traverse this rejection based on the current amendments.

Applicants acknowledge the Examiner's provisional rejection of claims 1-2, 6-7, 11-17, 44 and 48-50, under the doctrine of nonstatutory obviousness-type double patenting, over claims 1-2,

4-5, 9-15, 38 and 42-44 respectively of co-pending application 10/106,269.

No new matter has been added.

Claim Objections

The Examiner has objected to claims 3-6 as lacking appropriate 'colon' indicator for lists. Applicants have responsively amended these claims to obviate this rejection, and respectfully request withdrawal of this objection.

Rejection under 35 U.S.C. § 112 ¶2

The Examiner has rejected claims 1-17, 25, 44 and 48-52, under 35 U.S.C. § 112 ¶2 as being indefinite in the recitation of the term "disjunct."

Specifically, the Examiner states that the term "disjunct" is not clearly defined in the disclosure, and is therefore the term "disjunct phnenotypes" is ambiguous. The Examiner urges that for purposes of examination, the term "will mean distinct or different such that there is no overlap."

Applicants respectfully traverse this rejection, because applicants' usage of the term throughout the specification is in the art-recognized sense (including Webster's Dictionary) of 'characterized or marked by separation.' For example, the specification at page 16 recites "ill and health" as disjunct phenotypic classes, and additionally states that "tumor cell samples may be classified according to tumor type or staging of the tumor type" to provide disjunct phenotypic classes. Therefore, for purposes of the examination, Applicants contend that the term disjunct phenotypic class should mean phenotypically *distinct* classes. In particular embodiments, such distinct classes have no overlap, while in other embodiments there may be some aspect of overlap (e.g., stages of tumors overlap in the sense that the stages may be of all one tumor type) provided the phenotypic classes are still distinct (e.g., the tumor stages are still distinct).

Applicants, therefore, respectfully request withdrawal of this rejection.

Rejection under 35 U.S.C. § 102

The Examiner has rejected claims 1-4, 6-10 and 48, under 35 U.S.C. § 102(b) as being allegedly anticipated by Janousek et al. (*Molecular and General Genetics*, 250:483-490, 1996).

Specifically, the Examiner, after listing the text of claims 1-4, 6-10 and 48, states that Janousek teaches that "female sex suppression in M. Album males [male plants] is dependent on methylation of specific DNA sequences and can be heritably modified by hypomethylating drugs." In this context, the Examiner states that Janousek teaches that genomic "DNA was collected and stored" (allegedly Applicants' step (a)), that "sexual phenotype" was selected as the phenotype (allegedly Applicants' steps (b) and (c)), and that the plants were "divided into classes (one for each sex) based on the sex" (allegedly Applicants' step (d)). The Examiner additionally states that Janousek teaches that "the epigenetic features of interest include cytosine methylations" such as "CG doublets" and to a lesser extent "CNG triplets" (allegedly Applicants' step (e)). The Examiner further states that Janousek teaches methylation analysis (allegedly Applicants' step (f)), and teaches that the epigenetic feature of cytosine methylation (*e.g*, methylation of "CG doublets" and to a lesser extent "CNG triplets") can be used for "prediction of said phenotypic classes" (allegedly Applicants' step (g)). The Examiner states that the teaching of Janousek that "the epigenetic features of interest include cytosine methylations" such as "CG doublets" and to a lesser extent "CNG triplets" amounts to teaching that an initial epigenetic feature set (CGs and CNGs) "is narrowed to a new set of epigenetic features, namely hypomethylation of CG base pairs" (allegedly Applicants' step (h)). Further, citing Janousek at Figures 3 and 4, the Examiner urges that the Janousek "method is repeated several times" (presumably, but inappropriately, in reference to Applicants claim 2 that recites iterative repetition of steps (f) and (g) of claim 1). Finally, (but with no cited support from Janousek) the Examiner further urges that where "a decrease in the number of samples provided and [in] the amount of cytosine methylation that occurs, epigenetically-based prediction of the phenotypic classes of interest is likely to decrease" (this statement is presumably, but inappropriately, in reference to steps (g) and (h) of Applicants' claim 1, and to Applicants' claim 9 that recites a definition for relevant epigenetic feature

"wherein the relevant epigenetic feature or a combination of epigenetic features is relevant for epigenetically-based prediction of said phenotypic classes of interest when at least one of an accuracy and a significance of the epigenetically-based prediction of the phenotypic classes of interest is likely to decrease by exclusion of the corresponding epigenetic feature data of the epigenetic feature data set".

Applicants have made clarifying amendments to the claims to obviate this rejection. Specifically, independent claim 1 has been amended to recite "collecting and storing biological samples containing mammalian genomic DNA...." Support for this amendment can be found throughout the originally filed specification (*e.g.*, at Figures 1, 9, 10; page 19, in reference to Figure 1, Examples 1 and 2, etc.) including the claims (*e.g.*, claims 4, 5 and 6). No new matter has been added.

The amendment fundamentally distinguishes the presently claimed subject matter from that of Janousek, which is entirely limited to methylation analysis in plants. Significantly, as summarized in Janousek itself, there are *fundamental* differences between methylation in plants and mammals, including but not limited to the fact that in plants up to 30% of all cytosine residues is methylated at the C-5 position, and methylation in mammals is restricted to CG doublets, while in plants methylation also occurs at CNG triplets and even non-symmetrical DNA sequences. Therefore, regardless of how the teachings of Janousek are construed, one can reasonably extrapolate the teachings to mammalian cells and mammalian biology.

Applicants, therefore, respectfully request withdrawal of this anticipation rejection, which is not supportable by assertion of Janousek.

Rejections under 35 U.S.C. § 103

Janousek, in view of ***Curtis***:

The Examiner has rejected claims 1, 2, 10-16, 25, 44, and 52, under 35 U.S.C. § 103(a) as being allegedly obvious Janousek et al. (*Molecular and General Genetics*, 250:483-490, 1996) in view of Curtis et al. (Annals of Human Genetics., 65:95-107, Jan. 2001).

Specifically, the Examiner, after listing the text of claims 1, 2, 10-16, 25, 44, and 52, states that "Janousek teaches the method of identifying epigenetic features to deduce phenotypic properties," however does "not teach how to rank results or use machine learing classifiers to figure these accurate phenotypes." The Examiner states, however, that Curtis" use neural networks to classify between disease and multiple marker genotypes," that "a neural network is an example of a machine learning classifier," and that "the results in Curtis are ranked according to linkage to an inflicted mutation over the course of many generations" (citing Curtis at Table 4 on page 104).

Applicants respectfully traverse this rejection, because the asserted references alone or in combination, do not support a prima *facie case* of obviousness.

Applicants respectfully traverse this rejection based on the current amendments to claim 1. Specifically, as discussed above, independent claim 1 has been amended to recite "collecting and storing biological samples containing mammalian genomic DNA...." The amendment fundamentally distinguishes the presently claimed subject matter from that of Janousek, which is entirely limited to methylation analysis in plants. Additionally, the teachings of Curtis do not encompass epigenetic features or methylation, because the Curtis teachings are limited to artificial (*i.e.*, virtual) data sets comprising virtual single nucleotide polymorphisms (SNPs) (Curtis at page 99, first column; "then for each marker a single mutation event was modeled...."). Generations of virtual recombination were then made and a disease mutation introduced, followed by further virtual recombination to diminish linkage disequilibrium between the disease and SNP marker loci (the disease locus having been placed at a fixed map position relative to the SNP marker loci) and produce a dataset with varying degrees of linkage disequilibrium between the disease and marker loci (Curtis at page 99, second column).

Contrary to the Examiner's urging, Curtis does not teach use neural networks to classify between disease and multiple marker genotypes in the sense of the presently claimed invention. Rather, Curtis teaches that a "useful increase in power can be obtained in a [simulated] case controlled association study by using an artificial neural network to analyse data from multiple

SNPs simultaneously" (page 105, second column).. That is, Curtis teaches that, compared to analysis using single marker tests (either using just one single marker test or a combination of single marker tests), simultaneous analysis of multiple (*e.g.*, 2, 3 or 4) linked markers increases the power (or frequency of tests showing an association) by, or example 10% (*Id*). Contrary to the Examiner's urging, the data of Table 4 (cited by the Examiner) does not in fact show the results in Curtis are ranked according to linkage to an inflicted mutation over the course of many generations. Significantly, the "results" in Tables 3 and 4 do not show ranking of genetic (much less epigenetic) features in the sense of the present invention. Rather, the results, as discussed by Curtis in detail (beginning in the first column of page 104 and extending through the first column of page 105) illustrate, for each row of the table, the enhanced utility ("Overall test" column) of combining the neural network analysis ("Neural network" column) with the single marker test ("Single marker test" column). The Table also show that the extent of enhancement increases, relative to the single marker test, as one proceeds in the comparison from the use of one marker SNP mutation ("1" in the "Number of mutations" column) to two ("2" in the "Number of mutations" column), three ("3" in the "Number of mutations" column)or four ("4" in the "Number of mutations" column) SNP mutations. Therefore, there is no ranking of the different SNPs in the sense of the presently claims selection and ranking of epigenetic features. Moreover, as stated above, even if there were, the simulated data of Curtis relating to virtual SNP analysis (i.e., virtual genetic analysis) do not encompass epigenetic analysis including methylation analysis. The linkage and linkage disequilibrium analysis of Curtis is based on the utility of genetic chromosomal map linkage, and feature selection is, therefore, limited to map linkage as recognized by the Examiner. Such is not the case for the presently claimed epigenetic features.

Therefore, while Curtis, as construed by the Examiner may teach use of neural networks as machine learning classifiers, Curtis, alone or in combination with Janousek does not teach or otherwise reasonably suggest, the presently claimed method of identifying and selecting relevant epigenetic features to deduce phenotypic properties in mammalian cells or tissue. Plants are fundamentally different from mammalian cells, and neither Janousek nor Curtis, alone or in

combination, teaches selection of relevant epigenetic features to predict phenotypic disjunct phenotypic classes in mammalian cells or tissues.

Applicants, therefore, respectfully request withdrawal of this rejection.

Janousek, in view of ***Curtis***, and further in view of ***Spotorno***:

The Examiner has rejected claims 1, 10, 11, 13 and 17, under 35 U.S.C. § 103(a) as being allegedly obvious Janousek et al. (*Molecular and General Genetics*, 250:483-490, 1996) in view of Curtis et al. (Annals of Human Genetics., 65:95-107, Jan. 2001), and in further view of Spotorno et al. (*Evolution Biologica*, 4:37-62, 1990).

Janousek and Curtis have been discussed above.

Specifically, the Examiner, after listing the text of claims 1, 10, 11, 13 and 17, states that that neither Janousek nor Curtis teach the principal component analysis, but that Spotorno use principal component analysis to identify linkage between epigenetic and phenotypic analysis (citing Spotorno at Abstract

Applicants respectfully traverse this rejection based on the current amendments to independent claim 1 as discussed above. Applicants regard the assertion of Sportorno (which relates to rodent studies) as moot in view of the above-described claim 1 amendments and the fact that principal component analysis is recited in Applicants dependent claim 17, which depends serially from claim 13 and claim 1.

Applicants, therefore, respectfully request withdrawal of this rejection, because Applicants contend that presently amended independent claim 1 is free of the art

Nonstatutory Double Patenting Rejection

The Examiner has provisionally rejected claims 1-2, 6-7, 11-17, 44 and 48-50, under the doctrine of nonstatutory obviousness-type double patenting, over claims 1-2, 4-5, 9-15, 38 and 42-44 respectively of copending application 10/106,269.

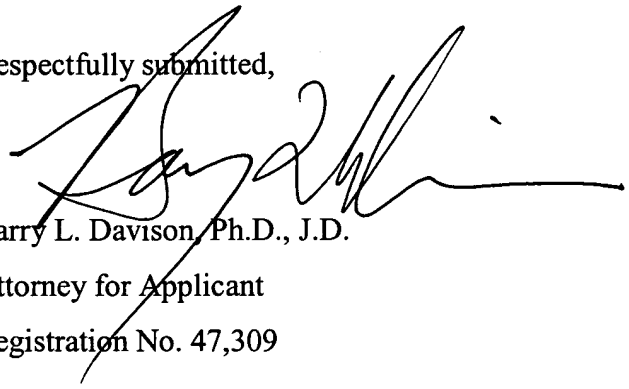
Applicants respectfully traverse this rejection based on the current amendments to

independent claim 1 as discussed above, and request withdrawal of this provisional double patenting rejection.

CONCLUSION

In view of the foregoing amendments and remarks, applicant respectfully requests allowance of the amended claim set provided herein above. The Examiner is encouraged to phone applicants' attorney, Barry L. Davison, to resolve any outstanding issues and expedite allowance of this application.

Respectfully submitted,



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